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10/552,965	07/21/2006	Francis Raul	279700US0PCT	1650

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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
09/24/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/552,965	RAUL ET AL.	
	Examiner	Art Unit	
	Charlesworth Rae	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claims 1-6 are currently pending in this application and are the subject of the Office action.

It is noted that for purposes of examination claims 1-4, which recite the term "The use," are being construed to be method of treatment claims.

Information Disclosure Statement

The information disclosure statement (IDS) and accompanying copies of non-patent references, filed 10/14/05, have been considered and made of record.

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 recite the term "The use," but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Rejection under 35 USC 101

35 USC 101 reads as follows

Whoever invents or discovers any new and useful process, machine, manufacturer, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-4 are rejected under 35 USC 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e. results in a claim which is not a proper process claim under 35 USC 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. V. Brenner,* 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for composition comprising geraniol for use in the blocking of the development and differentiation of certain tumor cells (e.g colon/leukemia/ hepatoma/melanoma cancer cells; see specification, page 2, lines 6-34), does not reasonably provide enablement for use of geraniol therapeutic compositions for blocking the development and differentiation of any and all tumor cells. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to the process of preparing and using therapeutic compositions comprising geraniol for blocking the development and differentiation of tumor cells.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical and medical arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmacologic, pharmaceutical, and clinical efficacy. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

Carnesecchi et al. teach that geraniol, a component of vegetable essential oils, sensitizes human colon cancer cell lines to 5-fluorouracil treatment, which is disclosed to be related to the disturbance of cellular morphological and functional differentiation (Carnesecchi et al. Geraniol, a component of plant essential oils, sensitizes human colon cancer cells. IARC Scientific Publications. 2002;156:407-409; **already made of record by applicant**).

Burke et al. (Bruke et al. Inhibition of pancreatic cancer growth by the dieatary isoprenoids farnesol and geraniol. Lipids. 1997; 32(2):151-6, abstract only) teach that fruits and vegetables have protective effects against many human cancers; isoprenoids are one class of phytochemicals which have antitumor activity, including dietary geraniol.

2. The breadth of the claims

The instant claims are relatively broad in scope. For example, claim 1 encompasses any and all tumor cells. The term *"blocking the development and differentiation of tumor cells"* is very broad as it encompasses both in vitro and in vivo treatment models; said term also encompasses any and all primary cancers as well as any and all sites of metastatic cancer. Also, claims 1-3 and 5 reasonably encompass compositions comprising any cytotoxic antitumoral agent plus geraniol (see specification, page 2, lines 27-34). Besides, the term geraniol encompasses synthetic and natural dietary sources of geraniol. Because the therapeutic response to be achieved would necessarily vary depending upon the specific type of tumor cell being targeted and the specific mode of action of the cytotoxic agent/agents utilized in the composition in combination with geraniol, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification discloses specific cytotoxic compounds for use in the geraniol therapeutic compositions and effective amounts of geraniol for blocking differention of tumor cells and potentiating the cytotoxic effect of an antitumoral agent both in vitro and in vivo, as well as dosing information for 5-FU (page 3, lines 1-36). Example 1 exemplifies the effect of geraniol ± 5-FU on colon cancer cells in vitro (page 4, line 32 to page 6, line 2; example 2 exemplifies the effect of geraniol on colon cancer cells functional differentiation in vitro; example 3 exemplifies the effect of geraniol and 5-

FU on colon cancer cell growth; example 4 exemplifies the effect of geraniol on colon cancer cell death in vitro; example 5 exemplifies the effect of geraniol on cellular uptake of 5-FU in vitro; and example 6 exemplifies the effect of geraniol on growing cancer cells and SW620 cells treated with 5-FU; example 7 exemplifies the effect of combined administration of geraniol and 5-FU on the growth of 5-FU resistant colonic tumor in mice (pages 4-11). Thus, the 'working examples" are limited to compositions of geraniol and 5-FU for use in *"blocking the development and differentiation of colon cancer cells."* Based on the instant disclosure, the applicant at best has provided specific direction or guidance only for a geraniol alone or in combination with 5-FU compositions for use in *"blocking the development and differentiation of colon cancer cells."* No reasonably specific guidance is provided concerning useful therapeutic protocols (e.g. dosages) or specific agents (including compounds of Table 1) for treating other cancers using compositions comprising geraniol in combination with cytotoxic agents except for 5-FU. In view of the complex mechanisms of action exhibited by the various classes of known cytotoxic agents, extrapolation of the exemplified in vitro data and in vivo mice data disclosed by applicant to other mammalian species with other cancers would reasonably require extensive experimentation.

4. The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, claims 1-5 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

Claim rejections – 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 5-6 are rejected under 35 USC 102(b) as being anticipated by Carnesecchi et al. Geraniol, a component of plant essential oils, sensitizes human colon cancer cells. IARC Scientific Publications. 2002;156:407-409, **already made of record by applicant**).

Carnesecchi et al. teach geraniol plus 5-fluorouracil, which reasonably must be administered a dosage form i.e. a composition (page 408, middle col., last paragraph). Instant claims 1-2, and 5 recite the term "geraniol;" while instant claim 6 recites the term "5-fluorouracil." The term "a cytotoxic antitumoral agent" as recited in claim 5 is satisfied in view of the teaching of 5-FU by Carnesecchi et al. Thus, claims 5-6 are anticipated by Carnesechhi et al.

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 are rejected under 103(a) as being unpatentable over Carnesecchi et al. Geraniol, a component of plant essential oils, sensitizes human colon cancer cells. IARC Scientific Publications. 2002;156:407-409, **already made of record by applicant)**, in further view of Bradley et al. (US Patent 5,919,815).

The discussion of Carnesecchi et al. in connection with the above rejection under 102(b) is incorporated by reference. Carnesecchi et al. does not teach irinotecan, oxaliplatin, or paclitaxel(Taxol).

Bradley et al. teach paclitaxel anti-cancer cocktails which may comprise two or more compounds selected from anti-cancer drugs, including fluorouracil (col. 13, line66-

67); irinotecan (col. 14, line 5); oxaliplatin (col. 15, line 49); and paclitaxel (Taxol) ((col. 13, line 32 to col. 18, line 65).

Based on the anti-cancer cocktails taught by Bradley et al. someone of skill in the art would have been motivated to combine the teaching of Carnesecchie et al and Bradley et al. to create the instant inventive concept. Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Claims 1-4 are rejected under 103(a) as being unpatentable over Carnesecchi et al. Geraniol, a component of plant essential oils, sensitizes human colon cancer cells. IARC Scientific Publications. 2002;156:407-409, **already made of record by applicant)**, in view of Bradley et al. (US patent 5,919,815), and in view of Bozec L. et al. Irinotecan-induced immune thrombocytopenia. Annals of Oncology. 1998;9:453-455.

Claims 1-4 for purposes of this rejection are being construed as method of treatment for using a therapeutic composition of geraniol.

Carnesecchi et al. teach geraniol plus 5-fluorouracil, which reasonably must be administered in a dosage form i.e. a composition (page 408, middle col., last paragraph).

Bradley et al. teach paclitaxel anti-cancer cocktails which may comprise two or more compounds selected from anti-cancer drugs, including fluorouracil (col. 13, line66-67); irinotecan (col. 14, line 5); oxaliplatin (col. 15, line 49); and paclitaxel (Taxol) ((col. 13, line 32 to col. 18, line 65). Instant claim 4 recites 5-fluorouracil, irnitocean,

oxaliplatinium, and Taxol. Bradley et al. teach that taxanes that are selective for treating central nervous system cancers, breast cancer, and colon cancer 9col. 4, lines 3-18). Instant claim 3 recites the term colorectal tumor cells, which is construed to overlap with colon cancer as taught by Bradley et al. Bradley et al. also teach that other cancers may be treated, including non-small cell lung cancer, melanoma cells and ovarian cancer cells (col. 13, lines 11-14); Bradley et al. also teach renal cancer (figure 7), prostate cancer (fig 8). Instant claim 3 recites the terms prostate cancer cells, digestive or aerodigestive cancer cells. The terms digestive or aerodigestive cancer cells as recited in claim 3 are construed to encompass colon cancer cells and non-small cell lung cancer as taught by Bradley. The terms *"blocking the development and differentiation of colon cancer cells" as recited in claim 1, and the term"therapeutic composition potentiating the cytotoxic effect of an antitumoral agent"* as recited in claim 2 are construed to be coextensive with the practice of the instant claimed invention. Bradley et al. does not teach hepatoma.

Bozec et al. disclose a method of treating comprising 5-FU and folinic acid and oxaliplatin (100 mg/m2) for Dukes D colon adenocarcimona with liver metastases, and its replacement with irinotecan (350 mg/m2) therapy due to hepatic recurrence (page 453, col. 1, last paragraph). Claim 3 recites the term "hepatoma cells" which is reasonably construed to encompass liver metastases.

Based on the anti-cancer cocktails taught by Bradley et al., someone of skill in the art would have been motivated to combine the teaching of Carnesecchie et al., and Bradley et al., and Bozec et al. to create the instant inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Relevant Art of Record

The below cited art reference made of record and relied upon is considered pertinent to applicant's invention.

Franklin et al. (US Patent Application Publication No. 20030157159) teach oral compositions for prevention and treatment of digestive tract infections in humans and animals comprising a single terpene, a terpene mixture or a liposome-terpene(s) composition (abstract). Franklin et al. teach that terpenes have been found to inhibit the growth of cancerous cells e.g. geraniol is disclosed to reduce/inhibit the growth of mammary tumors (page 1, para. 002 to page 4, para 0033).

Vamvakas et al. teach combination therapy of CPT-11 with 5-FU (Vamvakas et al. Irinotecan (CPT-11) in combination with infusional 5-fluorouracil and leucovorin (de Gramont regimen) as first-line treatment in patients with advanced colorectal cancer: a multicenter phase II study. Am J Clin Oncol. February, 2002. 25(1)65-70, abstract only).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

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13 September 2007
CER

BRIAN-YONG S. KWON
PRIMARY EXAMINER